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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/679,776	10/05/00	GRANSTEIN	R 2650/1F966-U

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EXAMINER	

ART UNIT	PAPER NUMBER
1632	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No.	Applicant(s)	
	09/679,776	GRANSTEIN, RICHARD D.	
	Examiner	Art Unit	
	Janice Li	1632	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-30 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-30 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Claims 1-30 are pending in the application and under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing tumor cell load in experimental fibrosarcoma by direct epidermal injection of total tumor cell RNA, or by subcutaneous injection of total tumor cell RNA-pulsed dendritic cells, does not reasonably provide enablement for reducing tumor cell load for all tumors, by all routes of introduction, or treating any tumor in human, and it does not reasonably provide enablement for protecting a subject from all pathogens, or for inducing tolerance to any and all antigens, The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to

the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

With respect to the claim breadth, the standard under 35 U.S.C. §112, first paragraph entails the determination of what the claims recite and what the claims mean as a whole. Claim 1 recites "a method of inducing an immune response to a pathogen". Concerning the breadth of the claims, although the claimed method is not limited to any particular application requiring any particular therapeutic effect, the specification teaches that the invention is for use in immunotherapy against a pathogen. When analyzing the enabled scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification, Claims 11 and 16 recite "a method for protecting a subject from a cancer", "inducing immune tolerance to an antigen". These claims clearly state an intended use as therapeutic methods. Claims 8, 13, and 24 recite "a pharmaceutical composition", "a vaccine". The claims clearly state the intended use of the composition "WHEN A COMPOUND OR COMPOSITION CLAIM IS LIMITED BY A PARTICULAR USE, ENABLEMENT OF THAT CLAIM SHOULD BE EVALUATED BASED ON THAT USE". (MPEP 2164.01c) When analyzing the enabled scope of the claims, the intended use is to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. "A pharmaceutical composition ...suitable for in vivo delivery to a human" is defined as a composition for therapeutic use, to prevent, diagnose, alleviate, treat, or cure a disease in human, therefore, will be evaluated by the standard. As such, the broadest reasonable interpretation of the

claimed invention properly encompasses gene therapy for cancer, for autoimmunity, for transplantation rejection, for allergic diseases in human. However, the specification does not provide an enabling disclosure to support the full scope of the claims.

In view of the guidance provided, the specification discloses by reduction to practice a reduced fibrosarcoma tumor cell load in mice by direct intradermal injection of total RNA of tumor cells, or by pulsing "epidermal cells" with total RNA of tumor cells, and introducing the pulsed cells subcutaneously to mice. However, the specification does not provide any evidence that the method would work for all types of tumor cells, for all pathogens, such as microorganisms, allergens, allograft antigens, and autoantigens, and by all routes of introduction of total tumor cell RNA. It does not provide guidance how to extend such treatment regimen to human or the methods would achieve the same effect in human.

In view of the state of the art in RNA transfected dendritic cells for cancer, it is not well developed and highly unpredictable. *Mitchell et al* (Curr Opin Mol Ther 2000 Apr;2:176-181) review, after the effective filing date of the instant application, the advantage and disadvantage for using RNA transfected dendritic cells as a relatively new approach for cancer vaccines. In spite of many advantages, the experience in using RNA material for gene therapy is limited to a few experimental tumor animal models, particularly, melanoma, and a human phase I clinical trial, which largely addresses the safety concern, far from protecting a human subject from cancer. The limitation is due to many known or unknown factors, for example, RNA could be degraded easily, have short half-life, and requires serum-free environment (not suitable

for intravenous delivery!) etc. No evidence of record or in the specification discloses that the method would be effective for other tumor-associated antigens, bacterial antigens, viral antigens, allergens or transplantation antigens.

In view of the state of the art for routes of genetic vaccine, *McCluskie et al* (Mol Med 1999 May;5:287-300) teach "ROUTE OF ADMINISTRATION OF PLASMID DNA VACCINES INFLUENCES THE STRENGTH AND NATURE OF IMMUNE RESPONSES IN MICE AND NON-HUMAN PRIMATES." (abstract) This teaching applies to RNA vaccines as well. In the instant case, when the targeting cell population is dendritic cells, intradermal delivery is advantageous because epidermis is rich in dendritic cells. It would require undue experimentation for other routes of delivery, particularly, intravenous injection of RNA would have been impossible to maintain the integrity of RNA even in a short period of time according to the knowledge of one ordinary skill in the art.

In view of the state of the art for tolerance induction, it involves complicated immune regulation. It is well known that the human immune system has a sophisticated system of self and non-self recognition and self-tolerance, a complex negative selection and autoreactive cell-elimination process. Induction of tolerance requires many factors working in concert, such as the type of antigen, the amount of antigen, the timing of antigen priming, and the state of host immune system etc. It would have required extensive undue experimentation for one skilled in the art to use the claimed invention to induce tolerance to any antigen, in any subject.

In view of the state of the art in gene therapy for human, *McCluskie et al* (Mol Med 1999 May;5:287-300) teach "UNFORTUNATELY, THE PROMISING RESULTS IN ANIMAL

MODELS HAVE NOT BEEN REALIZED IN HUMAN TRIALS AND CONSIDERABLE EFFORT IS NOW BEING FOCUSED AT UNDERSTANDING THIS DIFFERENCE AND DEVELOPING WAYS OF IMPROVING THE EFFICACY OF DNA VACCINES." (See 1st paragraph of the introduction) "HOWEVER, THE RESULTS IN MICE WERE NOT ALWAYS PREDICTIVE OF THOSE IN MONKEYS AND THIS IS LIKELY TRUE FOR HUMANS AS WELL. OPTIMAL DOSE AND IMMUNIZATION SCHEDULE WILL MOST LIKELY VARY BETWEEN SPECIES. IT IS NOT CLEAR WHETHER RESULTS IN NON-HUMAN PRIMATES WILL BE PREDICTIVE OF RESULTS IN HUMANS, THUS ADDITIONAL STUDIES ARE REQUIRED." (See abstract) Applicant is reminded of numerous factors complicating gene therapy, which have not been shown to be overcome by routine experimentation or resolved using animal models or *in vitro* studies. These factors include the fate of the nucleic acid itself (volume of distribution, rate of clearance, the fraction taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation etc.), the *in vivo* consequences of altered gene expression and protein function, the stability of the mRNA, the amount and stability of the protein produced, the compartmentalization and secretory fate of the protein within the cell. These factors differ dramatically based on the nucleic acid used, the protein being produced, the organs and tissues involved and the disease being treated. (*Eck et al,* pg81, col 2, paragraph 3, and page 82, col. 1, paragraph 2). *Boucher et al* (J Clin Invest 1999 Feb; 103:441-5) review that host cell resistance to foreign gene is another difficulty for successful gene therapy. "DESPITE AN IMPRESSIVE AMOUNT OF RESEARCH IN THIS AREA, THERE IS LITTLE EVIDENCE TO SUGGEST THAT AN EFFECTIVE GENE-TRANSFER APPROACH FOR THE TREATMENT OF CYSTIC FIBROSIS LUNG DISEASE IS IMMINENT. THE INABILITY TO PRODUCE SUCH A THERAPY REFLECTS IN PART THE LEARNING CURVE WITH RESPECT TO VECTOR TECHNOLOGY AND THE

FAILURE TO APPRECIATE THE CAPACITY OF THE AIRWAY EPITHELIAL CELLS TO DEFEND THEMSELVES AGAINST THE PENETRATION BY MOIETIES, INCLUDING GENE-THERAPY VECTORS, FROM THE OUTSIDE WORLD." Thus, it would require undue experimentation for any person skilled in the art to practice the claimed invention in humans.

Therefore, it is evident that at the time of the invention, the gene therapy practitioner, while acknowledging the significant potential of nucleic acids gene therapy, still recognized that such therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such a therapeutic regimen. Although the instant specification provides a brief review of a potential therapeutic use of the claimed methods, it is not enabled for its full scope because the specification does not disclose any particular embodiments reduced to practice in any disease other than experimental fibrosacoma or in human. In summary, the teachings and guidance present in the specification, as a whole, represent an initial investigation into the feasibility of the development of a useful means executing RNA gene therapy, which awaits further development to the practical level. Based upon the limited disclosure, the unpredictability of the art, the level of the skill, and the breadth of the claims, one of skill in the art would have been required to perform undue experimentation to practice the invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 11, 12, and 16-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-7, 11, 12, and 16-23 are incomplete because they do not recite that an immune response to a pathogen is induced, a subject is protected from..., or a tolerance to the antigen is induced.

Claims 1-7, 11, 12, and 16-23 are vague and indefinite because the claims are incomplete. The methods are directed to inducing an immune response to a pathogen, protecting a subject from a cancer, or inducing immune tolerance, however, it is unclear how mere administration relates to such effects. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

The recitation of "a tolerization route of administration" (claim 16) is vague and indefinite, because the claims do not make clear what is the tolerization route, and the specification does not teach how to determine or identify such route.

While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term "epidermal cells" in claims 1-7 is used by the claim to mean "antigen presenting cells in epidermis" (The specification defines

epidermal cells as "enriched for Langerhans cell content have been used as APCs" , page 2, lines 18-19), while the accepted meaning is "Langerhans cells or dendritic cells." For examining purpose, the examiner will treat "epidermal cells" as an alternative term for dendritic cells (DC) or antigen presenting cells (APC).

Claim 24, an "an" should proceed the recitation "antigen".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-3, 5, 7, 8, 9, 11, 24, and 28-30 are rejected under 35 U.S.C. 102(e) as being anticipated by *Nair et al* (IDS).

Claims 1-3, 5, and 7 are directed to a method comprising administering to epidermal cells total pathogen cell RNA *in vitro* or *in vivo*, wherein the pathogen is tumor, wherein an immune response to the pathogen is elicited. Claims 8, 9, 24, and 28-30 are directed to a composition comprising total RNA or mRNA or mRNA encoding an antigen of the pathogen cell, claim 11 is directed to a method for administering the total tumor cell RNA *in vivo*.

Nair et al teach a method comprising pulsing an antigen presenting cell *in vitro* with RNA obtained from a tumor cell or pathogen cell RNA (claims 1, 2, 6, 7, 8, 10, 14, and 16). *Nair et al* go on to TEACH "EVEN UNFRACTIONATED RNA PREPARATION (E.G., TOTAL

RNA OR POLY A+ RNA) CAN BE USED." (Column 3, lines 29-31) and "IF DESIRED, THE PREPARATION CAN BE FURTHER FRACTIONATED WITH RESPECT TO THE RNA (E.G., BY SUBTRACTIVE HYBRIDIZATION) SUCH THAT "TUMOR-SPECIFIC" OR "PATHOGEN-SPECIFIC RNA IS PRODUCED." The tumor RNA-pulsed APC are then administered to mice *in vivo*. The composition taught by *Nair et al* comprises the total pathogen cell RNA, total mRNA or RNA encoding an antigen, thus, meets the instant claim limitation. Therefore, *Nair et al* anticipate the instant claims.

Please **note** that in this and the following rejections, intended use limitations bear little weight on the determination of novelty of the invention. In this case, the claim limitation "is suitable for in vivo delivery to a human" or "for protecting a subject from a cancer" does not carry patentable weight in the determination of anticipation for the claimed products. This is because a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Claims 24 and 29 are rejected under 35 U.S.C. 102(a) as being anticipated by *Zhang et al* (Hum Gene Ther 1999 May 1;10:1151-61).

Claims 24 and 29 are directed to a composition comprising total mRNA of a pathogen cell. *Zhang et al* teach a composition comprising tumor cell total mRNA transfected dendritic cells. *Zhang et al* anticipate the instant claims.

Claims 24 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by *Qiu et al* (Gene Ther 1996;3:262-68).

Claims 24 and 30 are directed to a composition comprising mRNA encoding an antigen. *Qiu et al* teach a composition comprising tumor cell mRNA transcripted from cDNA encoding tumor antigen, and use of the composition for gene gun delivery to epidermis. *Zhang et al* anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 5, 7, 8, 9, 11, 12, 24, 28, and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Zhang et al* (Hum Gene Ther 1999 May 1;10:1151-61), taken with *Nair et al* (IDS).

Claims 1-3, 5, and 7 are directed to a method comprising administering to epidermal cells total pathogen cell RNA *in vitro* or *in vivo*, wherein the pathogen is a tumor, wherein an immune response to the pathogen is elicited. Claims 8, 9 24, 28, and 30 are directed to a composition comprising total RNA, or mRNA encoding an antigen of the pathogen cell, claims 11 and 12 are directed to a method for administering the total tumor cell RNA *in vivo*, wherein the method further comprising delivering an inflammatory cytokine to the subject.

Zhang et al teach transfecting dendritic cells with lymphotacin (an inflammatory cytokine), and incubating the transfected DC with mRNA of the tumor cells, wherein such cells are administered in vivo and induce a protective immune response in mice with experimental melanoma. *Zhang et al* do not teach use total cellular RNA or mRNA encoding the antigen only. However, before the effective filing date of the instant application, *Nair et al* (US 5853719) teach "FOR CONVENIENCE, AN RNA-ENRICHED TUMOR PREPARATION CAN BE USED IN LIEU OF PURIFIED RNA. THE INVENTION THUS CIRCUMVENTS THE NEED PURIFY RNA OR ISOLATE AND IDENTIFY A TUMOR ANTIGEN." "EVEN UNFRACTIONATED RNA PREPARATION (E.G. TOTAL RNA OR POLYA+RNA) CAN BE USED, IT IS NOT NECESSARY THAT A TUMOR OR PATHOGEN ANTIGEN BE IDENTIFIED" and "IF DESIRED, THE PREPARATION CAN BE FURTHER FRACTIONATED WITH RESPECT TO THE RNA (E.G., BY SUBTRACTIVE HYBRIDIZATION) SUCH THAT "TUMOR-SPECIFIC" OR "PATHOGEN-SPECIFIC RNA IS PRODUCED."

Therefore, it would have been obvious to one of ordinary skill in the art, at the time of the effective filing date, to substitute the mRNA taught by *Zhang et al*, with the total cellular RNA as taught by *Nair et al.* One of ordinary skill in the art would have been sufficiently motivated to do so for convenience, i.e. avoiding the trouble of purification step, or of identification of tumor pathogen, with a reasonable expectation of success. Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Claims 1-5, 7, 8, 9, 11, 24, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Qiu et al* (Gene Ther 1996;3:262-68), taken with *Nair et al* (IDS).

The claims 1-5, and 7 are directed to a method comprising administering to epidermal cells total pathogen cell RNA *in vitro* or *in vivo*, wherein the pathogen is a tumor, wherein the delivery is direct intradermal injection, wherein an immune response to the pathogen is elicited. Claims 8, 9, 24, 28, and 29 are directed to a pharmaceutical composition comprising total RNA or total mRNA of the pathogen cell, claim 11 is directed to a method for administering the total tumor cell RNA *in vivo*.

Qiu et al teach gene gun delivery to epidermis of mRNA encoding melanoma antigen (obtained by cDNA transcription), and inducing antibody response to the specific antigen in mice. *Qui et al* do not use a total pathogen RNA or total mRNA. However, before the effective filing date of the instant application, *Nair et al* (US 5853719) teach "FOR CONVENIENCE, AN RNA-ENRICHED TUMOR PREPARATION CAN BE USED IN LIEU OF PURIFIED RNA. THE INVENTION THUS CIRCUMVENTS THE NEED PURIFY RNA OR ISOLATE AND IDENTIFY A TUMOR ANTIGEN." "EVEN UNFRACTIONATED RNA PREPARATION (E.G. TOTAL RNA OR POLYA+RNA) CAN BE USED, IT IS NOT NECESSARY THAT A TUMOR OR PATHOGEN ANTIGEN BE IDENTIFIED."

Therefore, it would have been obvious to one of ordinary skill in the art, at the time the effective filing date, to substitute the mRNA taught by *Qiu et al*, with the total cellular RNA as taught by *Nair et al.* One of ordinary skill in the art would have been sufficiently motivated to do so for convenience, i.e. avoiding the trouble of purification step, or of identification of tumor pathogen, with a reasonable expectation of success. Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

No claim is allowed. Claims 6, 10, 13-23, 25-27 are free of cited prior art of record, because the cited prior art of record fails to teach or fairly suggest using fibrosarcoma model, delivery of the composition with an adjuvant, or via intravenous, intranasal routes, and a tolerization route. The cited art of the record does not teach a composition of RNA from an allergen, an autoantigen, or a transplantation antigen. However, these claims are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M Hauda can be reached on 703-305-6608. The fax numbers for the organization where this application or proceeding is assigned are 703-308-8724 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Kay Pinsky, whose telephone number is (703) 305-3553.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
June 15, 2001

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER